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**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: CELLULAR IMMUNOTHERAPY

(57) Abstract

Broadly, disclosed is a novel approach to the adoptive cellular therapy of HIV infection that exploits the potentially effective cellular immune response that is initially generated in HIV-infected individuals. One aspect is a method for preparing cells for treating patients afflicted with human immunodeficiency virus (HIV), which includes subjecting cytokine-producing cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free media for their expansion. The resulting therapeutic agent for treating patients afflicted with human immunodeficiency virus (HIV) includes in a pharmaceutically-acceptable carrier cytokine-producing cells having been produced by the step of subjecting cytokine-producing cells derived from lymph nodes excised from patients infected with HIV to mitogenic stimulation in serum-free media for their expansion. As another aspect of the present invention, disclosed is a method for treating patients afflicted with human immunodeficiency virus (HIV) which includes administering to the patient an effective amount of the therapeutic agent disclosed herein. The invention also is capable of inhibiting replication of HIV as measured by the viral load reductions exhibited by patients that receive the inventive therapeutic and in inducing an immunorestorative effect in HIV patients.

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# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

## PCT

NOTIFICATION CONCERNING
AMENDMENTS OF THE CLAIMS

(PCT Rule 62 and
Administrative Instructions, Section 417)

To:

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Office
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Crystal Plaza 2
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in its capacity as International Preliminary Examining Authority

| | |
|---|---|
| Date of mailing: 03 November 1997 (03.11.97) | |
| International application No.: PCT/US97/02309 | International filing date: 20 February 1997 (20.02.97) |
| Applicant: CIRA TECHNOLOGIES, INC. et al | |

The International Bureau hereby informs the International Preliminary Examining Authority that no amendments under Article 19 have been received by the International Bureau (Administrative Instructions, Section 417)

**The International Bureau of WIPO**
**34, chemin des Colombettes**
**1211 Geneva 20, Switzerland**

Facsimile No.: (41-22) 740.14.35

Authorised officer:

N. Lindner

Telephone No.: (41-22) 338.83.38

# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

## PCT

### NOTIFICATION OF ELECTION

(PCT Rule 61.2)

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| **Date of mailing** (day/month/year)<br>03 November 1997 (03.11.97) | |
| **International application No.**<br>PCT/US97/02309 | **Applicant's or agent's file reference**<br>CIR20013PC |
| **International filing date** (day/month/year)<br>20 February 1997 (20.02.97) | **Priority date** (day/month/year)<br>21 February 1996 (21.02.96) |
| **Applicant**<br>OLSEN, Richard, G. et al | |

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

17 September 1997 (17.09.97)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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| **The International Bureau of WIPO**<br>**34, chemin des Colombettes**<br>**1211 Geneva 20, Switzerland** | Authorized officer<br>N. Lindner |
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PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

**(PCT Article 36 and Rule 70)**

| Applicant's or agent's file reference CIR20013PC | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No. PCT/US97/02309 | International filing date *(day/month/year)* 20 FEBRUARY 1997 | Priority date *(day/month/year)* 21 FEBRUARY 1996 |
| International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet. | | |
| Applicant CIRA TECHNOLOGIES, INC. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 17 SEPTEMBER 1997 | 06 FEBRUARY 1998 |
| Name and mailing address of the IPEA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>RON SCHWADRON<br>Telephone No. (703) 308-0196 |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US97/02309

## I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

[X] the international application as originally filed.

[X] the description, pages 1-39 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____.
pages _____ , filed with the letter of _____.

[X] the claims, Nos. 1-41 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. NONE , filed with the demand.
Nos. NONE , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

[X] the drawings, sheets/~~fig~~ 1-6 , as originally filed.
sheets/~~fig~~ NONE , filed with the demand.
sheets/~~fig~~ NONE , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[X] the description, pages NONE.

[X] the claims, Nos. none.

[X] the drawings, sheets/~~fig~~ NONE.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US97/02309

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. STATEMENT

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-41 | YES |
| | Claims | NONE | NO |
| Inventive Step (IS) | Claims | NONE | YES |
| | Claims | 1-41 | NO |
| Industrial Applicability (IA) | Claims | 1-41 | YES |
| | Claims | NONE | NO |

2. CITATIONS AND EXPLANATIONS

Claims 1-41 lack an inventive step under PCT Article 33(3) as being obvious over Ochoa et al. (US 5,443,983) in view of prior art disclosed in the description (page 4, lines 19-22).

The claims are drawn to a therapeutic agent, method of making said cells and methods of using said cells. Ochoa et al. teach that T cells can be cultured with antiCD3 antibody and IL-2 (see Abstract) resulting in the generation of cells that can be used to treat AIDS (see column 1, first paragraph). Ochoa et al. teaches a therapeutic agent comprising said cells in a pharmaceutically acceptable carrier (see column 11, second paragraph). While Ochoa et al. teaches that these cells are LAK cells, because the cells are from the same source and treated in the same manner as the cells of the claimed invention they would be expected to contain cytokine producing cells. Cytokine producing T cells are a normal component of lymph nodes, because all T cells produce cytokines of one type or another. Furthermore, the description discloses that unfractionated lymph nodes were used as a source of cytokine-producing cells. Ochoa et al. teaches that the lymphocytes are preferably obtained from the individual (HIV positive AIDs patient) to be treated. While Ochoa et al. do not specifically teach the use of lymph node cells, Ochoa et al. does teach that the cells used as a starting product can be derived from any tissue which is a source of lymphocytes (lymph nodes). Furthermore, the description discloses that art recognized that lymph node derived cells would have a superior locomotor ability and ability to traffic to lymph nodes in comparison to PBL (page 4, lines 19-22). Ochoa et al. teach that any art known media (serum-free macrophage media) can be used to grow T cells as along as said media supports T cell growth (column 3, third paragraph). A routineer would have derived the particular dosage of Il-2 and antiCD3 antibody used in the instant invention by routine experimentation. Ochoa et al. teaches that said cells can be cultured with antiCD3 antibody and IL-2 for any desired period of time (see column 3, first paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because
Ochoa et al. teach that T cells can be cultured with antiCD3 (Continued on Supplemental Sheet.)

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1-41 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the following reasons.

The description does not disclose how to use the claimed compositions and methods for the treatment of HIV infection in vivo in humans. The claimed compositions and methods read on compositions, methods of making said compositions and methods for treatment which are used for the treatment of HIV infection in vivo in humans. The description has not enabled the breadth of the claimed invention in view of the teachings of the description because the use for the instant invention disclosed in the description is the in vivo treatment of disease in humans. The state of the art is such that is unpredictable in the absence of in vivo data as to how the instant invention could be used for the treatment of HIV infection in vivo in humans. The claims of the instant invention read on cells having an "immunorestorative effect on patients with HIV infection", however no data has been disclosed in the description indicating that the claimed cells or methods have such an effect on HIV infected patients. Immunorestorative as used in the claims could be interpreted as encompassing the restoration of the damaged immune system of an HIV infected patient to that of a normal immune system found in a healthy individual.

Regarding the use of the instant invention to treat HIV infection in vivo in humans, the art recognizes that immunotherapeutic approaches for the treatment of HIV infection in vivo in humans have been largely unsuccessful. The art recognizes that appropriate evidence is required in order to demonstrate that a particular agent can be used for the treatment of HIV infection in humans. No such evidence has been disclosed in the instant application and therefore it is unpredictable whether the method of the instant invention could be used to treat HIV infection in humans.

There is no guidance in the description as to how many cells need to be administered, at what timepoint said cells would be administered or how said cells would be administered to a particular patient in order to induce the claimed immunorestorative effect. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the description.

The description is not enabling for the claimed invention which uses "mitogenic stimulation" per se. The only mitogenic stimulation disclosed in the description is that mediated by treatment with IL-2 and anti-CD3 antibody. No evidence has been presented that other methods of mitogenic stimulation will result in cells which exhibit the particular properties as per disclosed (Continued on Supplemental Sheet.)

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII



CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(6): A01N 63/00, 1/02; C12N 5/00, 5/08, 5/02, 1/00, 1/02, 1/04; C07K 14/55, 16/28, and US Cl.: 424/93.7, 93.71, 93.1; 435/2, 325, 372.3, 373, 383, 384, 386, 405, 406; 530/351, 388.75

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
antibody and IL-2 (see Abstract) resulting in the generation of cells that can be used to treat AIDS. A routineer would have used the claimed method to derive any T cell population that expressed
CD3 (helper cells) because Ochoa et al. teach that CD3+ cells can be expanded using the claimed method.

---------- NEW CITATIONS ----------
NONE

VIII. CERTAIN OBSERVATIONS ON THE APPLICATION (Continued):
in pages 15-20 of the description. Therefore the description is not enabling for the instant invention.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/02309

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.7, 93.71, 93.1; 435/2, 325, 372.3, 373, 383, 384, 386, 405, 406; 530/351, 388.75

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS, EMBASE, DERWENT WPI, CHEM AB, APS search terms: author names, T cells, T lymphocytes, IL-2, CD3, antiCD3, antibody, HIV, in vitro, lymph nodes, helper, CD4

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 5,443,983 A (OCHOA ET AL.) 22 August 1995, see entire document. | 1-41 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | | | |
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| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
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| Date of the actual completion of the international search<br>02 JUNE 1997 | Date of mailing of the international search report<br>24 JUN 1997 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>RON SCHWADRON<br>Telephone No. (703) 308-0196 |

Form PCT/ISA/210 (second sheet)(July 1992)*

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/02309

A CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A01N 63/00, 1/02; C12N 5/00, 5/08, 5/02, 1/00, 1/02, 1/04; C07K 14/55, 16/28

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/93.7, 93.71, 93.1; 435/2, 325, 372.3, 373, 383, 384, 386, 405, 406; 530/351, 388.75